Review

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Embracing the Science of Motherhood: Pregnancy's Transformative Effects on the Central Nervous System and the Radiance of Maternal Hormones and Immune Responses

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Pregnancy is often thought of as a time of happiness and anticipation, however, for some women, it can bring about significant emotional distress and feelings of vulnerability. The physiological changes that occur during pregnancy, including hormonal fluctuations and alterations to the immune and physical systems, can affect various parts of the body, including the central nervous system (CNS). As a result, existing conditions may be intensified or new ones, such as neurologic or psychiatric disorders, may arise, exposing women to increased risk of life-threatening conditions or suicide, in the worst-case scenarios. Given the impact of pregnancy on CNS diseases, it is crucial for healthcare providers and patients alike to be aware of these potential effects. By understanding how pregnancy may affect the CNS, clinicians can take appropriate steps to ensure that women receive the care and support they need to minimize any negative outcomes for both the mother and the baby. This paper aims to review the available evidence on the impact of pregnancy on CNS diseases, including mental health conditions, from both the clinical and biomolecular perspectives. By illuminating this crucial subject, this study fosters a delicate understanding within both patients and healthcare providers, thereby paving the way for enhanced outcomes for women throughout their pregnancy journey and beyond.

Keywords: pregnancy; mental health; emotional distress; suicide; hormone; cytokine; complement; antibodies

Introduction

Pregnancy and its related central nervous system (CNS) complications are conditions classified within the field of women's neurology, namely the subspecialty of neurology related to the specific healthcare needs of women in different stages of their life [1,2]. There is compelling evidence indicating that pregnancy may elevate the likelihood of certain neurological disorders, such as cerebrovascular diseases and stroke, Alzheimer's disease (AD) and other dementias, Parkinson's disease (PD) and other movement disorders, epilepsy, multiple sclerosis (MS), and even depression and suicide [3–10]. Women's neurology incorporates a preventive approach to minimize illness and attempts to improve both the quality of life and outcomes in women with neurologic disorders [1]. During pregnancy, the intricate interplay between hormones and the immune players plays a pivotal role in the development of neurological diseases. The female body undergoes remarkable biological transformations that exert a profound influence on the endocrine and immune systems. This leads to fluctuations in the levels of specific hormones, such as human chorionic gonadotropin, estrogen, progesterone, relaxin, prolactin, and oxytocin as well as the modulation in innate and adaptive immune cells such as monocytes (MOs), macrophages (Mϕs), natural killer (NK) cells, effector T cells, regulatory T cells (Treg), invariant natural killer T (iNKT) cells, innate lymphoid cells (ILCs) and their effector products, such as glycoproteins, mixed lymphocyte reaction blocking factor (MLR-Bf), anti-paternal cytotoxic antibody (APCA), anti-idiotypic antibody (AITA), interleukin 6 (IL6), IL7, transforming growth factor beta 1 (TGFβ1), and complement proteins. They are all crucial for establishing and maintaining maternal-fetal tolerance and ensuring successful labor (Tables 1,2).

However, it is crucial to recognize that disturbances in the delicate balance of these hormones and the immune players during pregnancy can have far-reaching consequences, leading to the emergence of neurological symp-

toms and an elevated risk of developing various conditions such as stroke, epilepsy, MS, suicide, PD, and AD [11–20]. This sophisticated relationship between hormonal changes and immune responses during pregnancy has significant implications for the onset and progression of neurological diseases. In light of these considerations, it becomes essential for clinicians to carefully evaluate the safety of investigations or drugs administered before and during pregnancy, as well as during labor, delivery, and breastfeeding. The physiological condition of pregnancy introduces potential complications that must be considered. Consequently, certain medications may need to be discontinued before conception to mitigate any potential teratogenic effects on the developing fetus.

Moreover, it is important to acknowledge that pregnancy can have diverse effects on the clinical presentation of neurological diseases. Each case must be evaluated individually, considering the unique circumstances and the potential impact of hormonal and immune system alterations on the underlying condition. By recognizing the intricate relationship between hormones, immune responses, and neurological diseases during pregnancy, healthcare professionals can provide more informed care, considering the complexities and potential risks associated with this physiological state. A thorough understanding of these interconnections is crucial for ensuring the well-being of both the mother and the developing fetus.

In this comprehensive narrative review, we aim to explore the specific neurologic and psychiatric concerns that arise during pregnancy, focusing on the field of women's neurology and immunology. Our exploration will encompass a range of neurological conditions, examining them in detail and considering their varying severity and impact on both the mother and the developing fetus. We first examined the more severe and life-threatening conditions associated with pregnancy, ensuring a thorough understanding of their pathophysiology and clinical manifestations. This includes a comprehensive analysis of cerebrovascular disorders, such as strokes, transient ischemic attacks, and headache disorders, which has been linked to other neurological signs and symptoms and are expected to appear due to the various hormonal changes during the pregnancy [21–28]. Moving forward, we explored epilepsy and its management during pregnancy, considering the unique challenges it poses and the potential risks to both the mother and the developing fetus. Additionally, we discussed the complexities of dementia, movement disorders, MS, and their obscure relationship with pregnancy. Recognizing the importance of mental health, we addressed the impact of pregnancy on depression and suicide, casting light on the factors contributing to these conditions and discussing potential therapeutic approaches. Throughout our review, we emphasized the underlying pathophysiological mechanisms, clinical presentations, available treatment options, and the biomolecular basis of these pathological conditions associated with pregnancy. By comprehensively examining these topics, we aim to provide clinicians and researchers with a deeper understanding of the complexities and challenges faced in the space of women's neurology and immunology during pregnancy.

Cerebrovascular Disorders

Cerebrovascular disorders in pregnancy include failure of cerebral autoregulation systems: preeclampsia and eclampsia, reversible cerebral vasoconstriction syndrome (RCVS), posterior reversible encephalopathy syndrome (PRES); hemorrhagic and ischemic stroke; and cerebral sinus venous thrombosis (CSVT). These are all severe and even life-threatening conditions; therefore, it is crucial for neurologists to be aware of their potential association with pregnancy. They should be capable of promptly diagnosing and treating these illnesses using the least invasive and damaging approaches for both the mother and the fetus.

Preeclampsia, Eclampsia, RCVS, and PRES

Preeclampsia is defined as the new onset of persistent arterial hypertension (measured at least on two different occasions, 4 h apart from each other) starting from the 20th week of gestation, and accompanied by the new-onset of one of the following findings: proteinuria, impaired liver or renal function, thrombocytopenia, pulmonary edema, headaches unresponsive to paracetamol or visual symptoms (e.g., blurred vision, flashing lights, scotomata) [29]. It occurs in less than 10% of pregnancies and may be responsible for up to 15–16% of maternal deaths [28]. Preeclampsia may also occur in the postpartum period and the absence of any specific history of gestational hypertension; its pathophysiological mechanisms include genetic factors, impaired cerebral autoregulation, placental ischemia, immunologic factors, and abnormally increased sympathetic activity [28,30–34]. Severe preeclampsia is characterized by the presence of neurological symptoms like severe pulsatile headaches, and visual symptoms that can be misdiagnosed as migraine [30]. Usually, headache is of sudden new onset and presents in association with other neurological signs and symptoms, and with laboratory abnormalities [28]. Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome is a particular type of severe preeclampsia characterized by systemic involvement with hemolysis, elevated liver enzymes, and low platelets [35]. Preeclampsia with the occurrence of tonic-clonic, new-onset, epileptic seizures is called eclampsia, usually in the absence of any other causative conditions for the seizures, and is one of the more frequent causes of maternal deaths during pregnancy [29]. Patients with eclampsia may present with RCVS, which is a condition typical of the postpartum stage and is characterized by segmental narrowing of cerebral arteries, accompanied by thunderclap headaches, and usually reversible within three months

[28,30]. RCVS and cerebellar narrowing are also observed in patients with PRES. Together with RCVS, stroke (both hemorrhagic and ischemic types), cerebral sinus venous thrombosis and cervical artery dissection are neurological complications of preeclampsia and may represent frequent causes of death [1,28,30,36]. Neurologists should be aware of this group of heterogeneous symptoms so that they can easily recognize the syndrome and promptly treat it until it is reversible.

Management of preeclampsia and eclampsia include magnesium sulfate intravenous (i.v.) injection to prevent seizures during gestational hypertension. Severe hypertension is managed with labetalol, hydralazine, and nifedipine. Headache is currently treated using nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line, and nimodipine is used in headaches associated with RCVS [28,29,37]. Regarding seizure treatments, please refer to section 4 "Epilepsy".

Hemorrhagic Stroke

Hemorrhagic stroke may consist of subarachnoid hemorrhage (SAH—it occurs when there is bleeding into the space between the brain and the thin tissues that cover it, known as the arachnoid membrane) or intracranial hemorrhage (ICH). Both conditions may be favored by preeclampsia and eclampsia that cause aneurysm or arterial vascular malformation (AVM) rupture because of increased blood pressure levels [1,28]. Hemorrhagic stroke may occur during pregnancy and puerperium and may cause both the fetus and mother's death. SAH can also be due to vasospasm of arteries in RCVS, preeclampsia, or cerebral venous sinus thrombosis, and has a more favorable prognosis than the aneurysmal SAH [38]. Aneurysmal SAH is favored by hypertension, and the hemodynamic changes related to pregnancy may predispose to aneurysm formation [39]. In addition, the risk of aneurysm rupture tends to increase during gestational age, being the greatest at the 30–34th week of gestation [39].

The management of ruptured aneurysms requires neurosurgical or endovascular treatment and C-section delivery, based on gestational age [1,28]. Unruptured aneurysms should be carefully monitored and their treatment can be delayed, also based on their maximum diameter (usually, those more than 10 mm should be treated) [40]. Management of unruptured and ruptured AVM follows the same approach, although the treatment decision is more individualized and decided on a case-by-case basis, considering that the risk of rebleeding is higher once the AVM is ruptured [41]. Finally, the management of blood pressure in ICH should be aimed at keeping its initial levels under 160/110 mmHg, with subsequent further reductions using labetalol, methyldopa, or nifedipine at levels of approximately 140/90 mmHg [42].

Ischemic Stroke

Ischemic stroke risk progressively increases during pregnancy, being the highest in the third trimester and puerperium. The main stroke mechanisms in pregnancy are cardioembolic and large/small artery disease as in the general population, plus unusual causes such as cervical artery dissection, cardioembolism due to patent *foramen ovale*, RCVS, amniotic fluid embolism that can affect both mother and fetus and Moya-Moya disease [43,44].

The management of ischemic stroke during pregnancy requires acute revascularization with thrombolysis and/or mechanical thrombectomy. Thrombolysis has been proven not to be a teratogen, and the recombinant tissue plasminogen inhibitor does not cross the placenta [45]. The benefit of thrombolysis should always outweigh the risk of uterine hemorrhage. In the case of recent surgery, within the previous two weeks, thrombolysis is riskier. In case of stroke after preeclampsia or eclampsia, the risk of bleeding is increased, and thrombolysis should be discussed case by case [45], to avoid hemorrhagic complications. Mechanical thrombectomy is well tolerated in pregnancy and is mostly used in cases of large vessel occlusion, as per current guidelines [46].

Choriocarcinoma-Induced Stroke

Choriocarcinoma is a rare and aggressive tumor that originates from the fetal trophoblastic tissue and typically infiltrates the maternal uterine blood vessels [47]. This highly vascular tumor can spread rapidly throughout the mother's body, making it a serious and potentially life-threatening condition [47–49].

One of the significant neurological complications associated with choriocarcinoma is the high incidence of cerebral metastatic lesions [48,49]. These lesions can take many forms, including embolic stroke, SAH, subdural or intracerebral hematoma, and hemorrhagic intraspinal mass [49–51]. An embolic stroke occurs when a blood clot or other debris travels through the bloodstream and blocks a blood vessel in the brain, leading to a loss of blood flow and subsequent damage to the brain tissue. In the case of choriocarcinoma, the tumor's ability to invade blood vessels makes it more likely that blood clots or other materials will dislodge and travel to the brain, resulting in an embolic stroke [52,53].

SAH, as mentioned above (Section 2.2), is often caused by the rupture of a blood vessel in the brain, and choriocarcinoma can contribute to this by causing the blood vessels to become weak and more prone to rupture [54].

A subdural or intracerebral hematoma occurs when there is bleeding within the brain tissue itself or in the space between the brain and its protective covering. Choriocarcinoma can contribute to these types of hemorrhages by disrupting the normal blood flow and making the blood vessels more susceptible to injury. As such the intracerebral and SAH have been reported in pregnancy [55,56].

A hemorrhagic intraspinal mass is a rare but potentially serious complication of choriocarcinoma. This occurs when the tumor invades the spinal cord and causes bleeding within the cord itself, leading to nerve damage and potential paralysis. The acute onset of paraplegia has been linked to pregnancy [57]. Overall, choriocarcinoma-induced stroke is a complex and challenging condition that requires careful management by a team of specialists. Early diagnosis and treatment are crucial to prevent serious neurological complications and improve patient outcomes.

Cerebral Sinus Venous Thrombosis

CSVT can present during pregnancy or in the postpartum period and is facilitated by hypercoagulability, iron deficiency, and the stress induced by delivery [58]. It may manifest as headache, papilledema, seizures, and/or visual disturbances [1]. Diagnosis should be aimed at the individuation and correction of any possible other risk factors contributing to venous thrombosis, including genetic causes of hypercoagulability and infections [28]. Other concurrent causes may be higher maternal age, preeclampsia, hyperemesis gravidarum, and C-section delivery [59].

The management of cerebral sinus venous thrombosis during pregnancy is anticoagulation with low-molecular-weight heparin (LMWH), which should be stopped 12–24 h before delivery, then re-started in the puerperium [1,28]. Warfarin is generally contraindicated in pregnancy and there is no evidence of the usage of novel oral anticoagulants [1]. LMWH is well tolerated during breastfeeding as well as warfarin [60].

Headache Disorders

Primary Headache Disorders: Migraine

Primary headache disorders, and more specifically migraines (with and without aura), are one of the most frequent diseases in pregnancy involving up to 17% of pregnancies [25]. It has been postulated that the hormonal changes, and mainly the increase of estrogens, associated with pregnancy may hypothetically prevent migraine attacks, however, high estrogen states are a trigger for migraine with aura [61]. Migraine in pregnancy is not difficult to diagnose, and no supportive neuroimaging techniques are required. However, the most challenging issue is related to its pharmacological management because of the side effects of the most used drugs. More importantly, even if migraine treatment with pharmacological drugs is possibly associated with side effects, it is worth considering that its undertreatment may cause further complications for the mother, such as poor nutrition, electrolyte imbalances and dehydration (often caused by hyperemesis), excessive absenteeism from work, and reduced mental health [1,62]. Finally, migraine in pregnancy is associated with an increased risk of preeclampsia and preterm birth or low birth weight [63].

Before discussing the acute management of headaches with drugs, it is important to focus on migraine prevention. Prevention starts with lifestyle and is mainly based on hygienic measures to ensure adequate nutrition, hydration, and sleep [1]. It is safe to use oral magnesium supplements as a prophylactic measure [64]. Pericranial nerve block with lidocaine or botulinum toxin type A injections can be considered for patients unwilling to start oral pharmacological treatments [65,66]. Drugs that can be used for the prevention of migraines are beta-blockers, which are relatively safe throughout pregnancy, except for the delivery stage, where they have been associated with hypoglycemia and bradycardia in the fetus [67]. Topiramate and valproic acid are contraindicated because of their intrinsic risk of congenital malformations [1,62]. Amitriptyline and cyproheptadine in selected patients may be used, although the former has been associated with an increased risk of congenital malformation, and the latter has scarce preventive efficacy for migraine [62].

Regarding the management of acute migraine attacks, NSAIDs are contraindicated after 20 weeks of gestation (as per the Food and Drug Administration (FDA) recommendations) because of the increased risk of renal injury and oligohydramnios in the fetus [1,68]. It should also be borne in mind that NSAIDs administered after 30 weeks of gestation are associated with an increased risk of premature closure of the *ductus arteriosus* in the fetus [1]. Paracetamol/acetaminophen is a safe analgesic during pregnancy and can be used for migraine treatment. However, recent studies have suggested that paracetamol/acetaminophen may be associated with the development of asthma, attention deficit hyperactivity disorder, and other developmental disorders in children [69,70]. Second line metoclopramide plus diphenhydramine can be used, being even more effective than codeine to treat headaches in pregnancy, in case of previous treatment failure with paracetamol/acetaminophen [71]. Metoclopramide (anti-dopaminergic) seems not to be associated with higher risks of congenital malformations, abortion, or stillbirths [1,72]. Diphenhydramine is a first-generation anti-H1 antihistaminic and is safe during pregnancy [73]. Prochlorperazine (as metoclopramide), belongs to the class of anti-dopaminergic drugs and can be used to manage headaches, although evidence for metoclopramide in pregnancy is more robust [74]. Other second-line drugs including triptans have not shown an increased risk of congenital malformations, although studies have documented a possible risk of premature birth [62]. Drugs such as valproic acid are contraindicated in pregnancy due to their teratogenic effect on the fetus; ergot derivatives (e.g., dihydroergotamine) are associated with an increased risk of spontaneous abortion; finally, magnesium can be used for i.v. injection acutely, but prolonged i.v. administration for more than 5 consecutive days may be associated with teratogenic effects on the skeleton [62,75].

Secondary Headache Disorders

Secondary headaches are also possible during pregnancy, and more importantly, patients with migraines may also develop secondary headaches. The most common cause of secondary headaches in pregnancy is arterial hypertension and related disorders, such as preeclampsia and eclampsia, as described in section [1]. Other causes of secondary headaches are the same as in the general population, namely CSVT, RCVS, ICH, idiopathic intracranial hypertension, infections, and finally pituitary apoplexy (rare) [27]. However, all secondary headaches may have specific neurologic, laboratoristic, and neuroimaging-associated abnormalities.

Epilepsy

As for primary headache disorders, epilepsy is frequent in pregnancy and the most challenging issue is not its diagnosis, but rather the prevention and acute management of seizures with drugs, given their teratogen effects. Preeclampsia is a risk factor for seizures *per se*, and in general pregnant women are at higher risk of developing seizures due to the hormonal, sleep, stress-related, antiepileptic drug (AED) metabolism, and blood pressure changes associated with pregnancy [76]. In addition, both convulsive and nonconvulsive seizures are associated with fetal hypoxia and acidosis, preterm birth, low birth weight, and ultimately abortion and fetal loss [1]. Given these premises, seizure treatment is warranted during pregnancy. Prevention of congenital teratogenic effects of antiseizure medications starts with pregnancy planning in women with a longstanding diagnosis of epilepsy, so that they can reduce or even stop the antiepileptic drugs (AEDs) in advance. In addition, folic acid is recommended for all epileptic and childbearing women at 0.4 mg/day, even if they are not actively planning a pregnancy [77]. Regarding the teratogenic effects of AEDs, it has been suggested that valproic acid is the most teratogenic drug, followed by carbamazepine, whereas phenytoin and lamotrigine are less associated with congenital malformations [76]. In general, polytherapy causes more teratogenic effects than monotherapy, and this is more valid for treatments including valproic acid and lamotrigine than carbamazepine. There is a direct relationship between the dose of these AEDs and the risk of congenital malformations [76]. Overall, valproic acid is associated with neural tube defects, facial clefts, and hypospadias (in order of frequency, from more to less frequent), phenytoin and carbamazepine may cause cleft palate and phenobarbital may cause cardiac malformations [76]. Other than the direct teratogenic effect, it has been shown that neonates born to women with epilepsy on AEDs (mostly valproic acid and carbamazepine) tend to show an increased risk of low weight at birth and reduced APGAR scores at birth [78]. Pregnancy changes are associated with increased clearance (and so decreased blood concentration) of lamotrigine, phenytoin, and carbamazepine, and a decrease in the levels of levetiracetam and oxcarbazepine [78]. As a direct consequence of such chemical changes, the frequency of seizures may increase. It is therefore suggested that the plasma AED levels should be strictly monitored during and after the pregnancy as abrupt increases in AED levels develop the frequent toxicity [76]. Hence, in the postpartum phase, AED levels should be reduced to prepartum levels, sleep deprivation should be avoided, and breastfeeding should be encouraged to prevent any type of possibly related complications [1,76].

Alzheimer's Disease and Other Dementias

AD is a neurodegenerative disorder that affects millions of people worldwide [79]. It is a progressive condition that causes memory loss, cognitive decline, and behavioral changes [80]. However, there have been reported cases of AD and other related dementias occurring in pregnant women [18,81]. Although the exact cause of AD and dementia during pregnancy is not fully understood, studies suggest that the immunosuppression that occurs during pregnancy may play a role [18,81]. Studies have shown that changes in the immune system during pregnancy can lead to an increase in inflammatory markers, (e.g., IL6 and IL17) in the brain, which are also present in AD and dementia [82–85]. These inflammatory markers can damage brain cells and contribute to the development of dementia.

Other factors that may contribute to the development of dementia during pregnancy include hormonal changes. For example, during pregnancy, estrogen and progesterone levels increase, which may affect the brain and increase the risk of developing dementia [86–88]. Another possible factor is stress, which has been linked to pregnancy and increased risk of dementia [89,90]. Pregnancy can be a stressful time, and the stress of pregnancy could potentially contribute to the development of dementia in some women with premorbid undiagnosed cognitive complaints [90,91]. In addition, certain medical conditions that can occur during pregnancy, such as preeclampsia, epilepsy, or gestational diabetes, have also been linked to an increased risk of cognitive decline and dementia later in life [92,93].

Despite these potential risk factors, it is important to note that dementia during pregnancy is extremely rare and is likely due to a combination of factors, including immunosuppression, hormonal imbalances, stress, and other existing indispositions during the pregnancy. However, further research in this area could help to better understand the connection between pregnancy and the development of cognitive deficits.

Movement Disorders

It is important to distinguish between the management of movement disorders that arise during pregnancy (e.g., chorea gravidarum, restless leg syndrome (RLS), and

ataxia) and the management of preexisting movement disorders, i.e., PD, Huntington's disease (HD), and ataxia during pregnancy [94].

Movement Disorders Arising during Pregnancy

Chorea gravidarum is defined as the onset during pregnancy of choreic movements, namely irregular and purposeless movements, slower than myoclonus, that flit from one body part to another in a chaotic pattern [94,95]. It is more frequent in the first trimester (50% of cases) and tends to reduce and/or disappear with complete recovery by the time of delivery [96,97]. Interestingly, it may recur in the following pregnancies [98]. Different from cerebrovascular conditions, it is not an emergency or life-threatening condition, but it may be associated with complications such as myoglobinuria, hyperthermia, and rhabdomyolysis, which in selected cases may lead to death [94]. The true pathophysiological mechanisms are, to date, still largely unknown. In the past, an increased incidence of chorea gravidarum has been reported in patients who had a previous diagnosis of Sydenham's chorea (e.g., chorea associated with rheumatic fever) or with a previous history of autoimmune conditions, encephalitis, or syphilis [99]. Within the spectrum of chorea gravidarum, 50% of cases are idiopathic and the remaining 50% are usually secondary to thyroid disorders, drugs, other neurological diseases (Wilson's disease or HD, stroke), and systemic autoimmune diseases (systemic lupus erythematosus, anti-phospholipid syndrome) [100]. During pregnancy, increased estrogen levels play a crucial role in the pathophysiology of chorea. Estrogens are associated with the synthesis of dopamine receptors in the striatum, and then favor the development of chorea in selected patients with an impairment in the basal ganglia circuitry for various reasons, (e.g., autoimmune, genetic, parainfectious, vascular) [94]. Other than the treatment for the underlying cause of chorea, when identified, which varies from case to case, the symptomatic treatment is aimed at reducing the intensity of choreic movements, only when they significantly and negatively impact the patient's quality of life. Dopamine receptor blockers and dopamine depleting agents are both teratogens and are usually discouraged during pregnancy. Only in case of significant patient discomfort, the dopamine receptor blockers haloperidol and chlorpromazine can be used at the minimum effective dose and for the shortest time, but always after the first trimester [101].

RLS, defined as the unpleasant or uncomfortable sensation in the legs and an irresistible urge to move them [102], is one of the most frequent conditions within the field of movement disorders occurring in pregnancy. RLS associated with pregnancy belongs to the secondary forms of RLS (e.g., secondary to a given disease or condition, namely PD, iron deficiency, uremia, diabetes, hypothyroidism, or drugs), whereas idiopathic RLS occurs without any associated diseases, and may present with a positive family history [103]. Hormonal changes in prolactin, estradiol, and progesterone levels during pregnancy may be associated with RLS, and their rapid drop after delivery is usually associated with its resolution [104,105]. Conditions associated with pregnancy that may favor the occurrence of RLS are iron deficiency, low ferritin and folic acid levels, hypothyroidism, and the occurrence of RLS during a previous pregnancy [94]. Usually, symptoms are transient and tend to resolve after delivery [106]. However, symptoms occasionally appear for the first time during pregnancy and persist as idiopathic RLS, but in some cases, they may persist even after pregnancy [106]. Simple hygienic measures may help prevent RLS during pregnancy, such as avoiding caffeine and alcoholic beverages, massaging the legs, and performing specific physical exercises [94]. This will help reduce the discomfort associated with RLS. Other safe strategies may include iron i.v. repletion in cases of documented iron deficiency [107]. Pharmacological treatment is usually discouraged in pregnancy and is used only if the symptoms are unbearable and lead to significant discomfort for the patient. Approved drugs for treating RLS in the general population are gabapentin, dopamine agonists (ropinirole, rotigotine, pramipexole), and levodopa, and they should be given at the lowest dosage and for the least time possible, given the still unknown deleterious effects on the fetus [108]. When starting a given drug treatment in RLS, the risk of the so-called augmentation phenomenon, namely the occurrence of symptoms at least 2 h ahead than previously with intensification and spread outside the legs in a caudal-cranial direction, should be considered [109]. Gabapentin is the drug of the first choice, given its safety profile and the relatively low risk of augmentation [110]. Carbidopa/levodopa can be considered only as a second choice, because the long-term effects on the fetus are unknown, and the augmentation phenomenon is more frequently observed than when using gabapentin [94]. Lastly, dopamine agonists are generally not used because of their possible teratogenic effects.

Acute ataxia occurring during pregnancy deserves a dedicated workup, mainly to exclude cerebrovascular and neoplastic conditions. Other relatively common causes of ataxia in pregnancy are nutritional deficits, mainly of group B vitamins (B1), associated with hyperemesis gravidarum, which causes the so-called Wernicke encephalopathy [94]. In this case, vitamin B1 should be reintegrated i.v. and/or i.m. as soon as possible, given the potentially fatal complication of Wernicke's disease.

The Management of Pre-Existing Movement Disorders during Pregnancy

Patients with chronic conditions such as PD, HD, ataxia, and tremor may be of childbearing age. Regarding PD, mainly in the forms of young (<40 years old) and early disease onset (<50 years old), there may need to be further guidance on which medications are allowed

during the disease course. Although the data are scarce, the safest medication for the fetus is carbidopa/levodopa, even if long-term studies on the effect of this drug on the fetus are not yet available [94,111]. HD is an autosomal dominant fatal neurodegenerative disorder with complete penetrance, classified within the repeat expansion disorders and affecting a CAG triplet. Each generation will typically have more repeats with an earlier disease at onset [94,112]. HD may affect women of childbearing age, and genetic counseling and prenatal testing is fundamental. However, chronic symptoms can be managed with haloperidol and chlorpromazine during pregnancy [113]. Genetic forms of ataxia, namely autosomal dominant spinocerebellar ataxias (SCAs) and Friedreich's ataxia (FA–autosomal recessive), may affect women of childbearing age. Genetic counseling and family planning are highly recommended in these patients.

Multiple Sclerosis

MS is a disease that is highly prevalent in young females who are of childbearing age. It is well-known that pregnancy and its related hormonal changes have a protective role on MS-related disease activity, with a reduction in relapses mainly in the third trimester, and an increased risk of new relapses in the postpartum phase [1,114]. In the last few decades, significant progress has been made in the disease-modifying immune-therapies for MS, with many new drugs being introduced in the market in recent years. These drugs play an immune-suppressive role, acting at different levels of the immune system. Given these premises, the first important aspect to consider is the safety of disease-modifying treatment discontinuation in pregnancy. It has been shown that, in the case of mild disease forms, the discontinuation of disease-modifying treatments may be safe, and does not increase the risk of relapses in the immediate postpartum phase [114]. Data on the use of disease-modifying treatments in pregnancy in MS are more robust for the drugs that have existed on the market for a long time, and there are less available data for the most recent ones. Glatiramer acetate and interferon-beta have a modest disease-modifying effect, and although they are overall safe in pregnancy, the evidence supporting their use is lower than the benefit offered from the natural protection offered by pregnancy on women with MS [1]. Dimethyl fumarate is minimally toxic during pregnancy, however, teriflunomide is significantly toxic in animal fetuses and should be avoided during pregnancy [114,115]. Fingolimod and natalizumab, despite being very effective drugs, are potentially teratogenic, and in both cases, pregnancy does not protect against relapses after cessation, therefore, they are contraindicated [114]. Rituximab and ocrelizumab have been associated with the reduction of B cells in the fetus after exposure during the second and third trimesters. Hence, it has been suggested to stop such treatment during pregnancy [114]. Finally, alemtuzumab is associated with autoimmune thyroiditis which may occur up to 4 years after the last infusion, therefore, it cannot be used in pregnancy (and even in women with childbearing interests) [114]. Relapses are rare in pregnancy, but if they occur, they may be treated with intravenous steroids only after the first trimester, given their possible intrinsic teratogenic effect [114]. In the first trimester, plasma exchange is the preferred option, given the increased thrombotic risk of intravenous immunoglobulin (IVIG) administration [114].

Beyond the Stereotypes

Pregnancy is a crucial period in a woman's life, and it is common for women to experience mood and anxiety disorders during this time. However, when a pregnant woman has a history of psychiatric disorders, the risks for both the mother and fetus increase. Bipolar disorder, affective psychosis, and schizophrenia are three psychiatric disorders that can have significant impacts on pregnant women and their offspring [116].

Bipolar disorder, also known as manic-depressive illness, is a mood disorder characterized by episodes of elevated or irritable mood (mania or hypomania) and depressive episodes. Women with bipolar disorder are at an increased risk of relapse during pregnancy, and the use of mood stabilizers and antipsychotic medications may be necessary to manage symptoms [117]. However, these medications can also have adverse effects on the developing fetus, such as congenital malformations and neurobehavioral problems [118].

Affective psychosis is a type of psychotic disorder that occurs in the context of a mood episode, such as mania or depression. Symptoms of affective psychosis include delusions, hallucinations, and disordered thinking. Approximately 1 in 13 women experience a new onset of a major depressive episode during pregnancy and 1 in 7 experience an episode postpartum [119,120]. Women with affective psychosis may require antipsychotic medications during pregnancy to manage their symptoms.

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. Symptoms of schizophrenia include delusions, hallucinations, disordered thinking, and disorganized behavior. Women with schizophrenia are at an increased risk of relapse during pregnancy, and the use of antipsychotic medications may be necessary to manage symptoms. However, some antipsychotic medications are associated with an increased risk of congenital malformations, gestational diabetes, preterm birth, and low birth weight [121–123].

In addition to the risks associated with medication use, psychiatric disorders during pregnancy can also lead to other adverse outcomes. For example, women with bipolar disorder or schizophrenia may face increased risks due to preeclampsia and their babies may be more likely to be born preterm [124,125]. Moreover, infants born to women

with these disorders may face an increased risk of neonatal complications, including respiratory distress and admission to the neonatal intensive care unit [126].

It is essential for pregnant women with a history of bipolar disorder, affective psychosis, or schizophrenia to receive specialized prenatal care from a team of healthcare providers, including a psychiatrist, obstetrician/gynecologist, and neonatologist. The healthcare team can develop an individualized treatment plan that balances the risks and benefits of medication use and provides appropriate monitoring for both the mother and the fetus. With proper management, women with these disorders can have successful pregnancies and healthy infants.

Suicide

Suicide during pregnancy and postpartum is a serious and often overlooked issue that has significant implications for both the mother and the unborn child [127–130]. Women who experience complications during their pregnancy, such as miscarriage, preterm labor, fetal abnormalities, psychiatric illness, depression, anxiety, a lack of social support, sleep disturbances, and relationship problems, may be at increased risk of suicidal ideation and behavior [129,131–144].

Treatment for mental health issues during pregnancy typically involves a combination of therapy and medication. Antidepressants and antipsychotics are effective in treating depression and bipolar disorder, but their use during pregnancy must be carefully monitored because of potential risks to the fetus [144]. Psychotherapy, such as cognitive-behavioral and interpersonal therapies can also be effective in treating mental health conditions during pregnancy.

Overall, suicide during pregnancy is a serious and preventable issue that requires increased awareness and social support. Therefore, it is suggested to continuously monitor pregnant women for signs of suicidal ideation and behavior. This involves regularly assessing their mental health and risk factors for suicide, such as past suicide attempts, substance abuse, and a lack of social support. If a woman expresses suicidal thoughts, clinicians must take these concerns seriously and provide appropriate care and support.

Hormones and Inflammation

During pregnancy, a woman's body undergoes significant biological changes that have a profound impact on various aspects of the endocrinological and immunological responses. The resulting alterations in the levels of certain hormones, (e.g., human chorionic gonadotropin, estrogen, progesterone, relaxin, prolactin, and oxytocin) and innate and adaptive immune responses play a crucial role in regulating the pregnancy and the nervous system. However, the alteration in the levels of such hormones triggers several neurological symptoms and increases the risk of developing stroke, epilepsy, MS, depression, PD, and AD in different gestational windows of pregnancy [11–20].

During the first trimester, the hormone levels, (e.g., progesterone, estrogen, human chorionic gonadotropin, and thyroid) increase rapidly. These hormones are secreted by the ovaries and placenta. The main function of progesterone is to maintain the pregnancy by preventing uterine contractions and estrogen is to promote the growth and development of the uterus. The hormone levels fluctuation during the first trimester can have both positive and negative effects on neurological symptoms and diseases. For instance, increased levels of estrogen and progesterone have been shown to have a protective effect on the brain by reducing inflammation and promoting nerve cell growth. However, these hormones can also cause neurological symptoms such as mood swings, headaches, dizziness, and nausea, which are common in the first trimester. In addition, changes in thyroid hormone levels can affect the neurological system. Low levels of thyroid hormone can cause fatigue, depression, and impaired memory, whereas high levels can cause anxiety and nervousness. The other symptoms associated with these first trimester hormones include morning sickness, fatigue, breast tenderness, frequent urination, nausea, and vomiting (Table 1, Ref. [88,145–189]).

During the second trimester, the hormone levels continue to rise, but at a slower pace than in the first trimester. The placenta takes over the production of estrogen and progesterone from the ovaries. Estrogen levels continue to increase and play a vital role in the development of the fetus and the preparation of the body for childbirth. At this stage, hormones play a critical role in fetal brain development. For instance, estrogen promotes the growth and development of the fetal brain, while progesterone maintains the pregnancy. Symptoms associated with the second trimester include increased appetite, weight gain, and fetal movement. The increased appetite and weight gain are due to metabolic changes in the body, while fetal movement is a sign of the developing nervous system. However, hormonal fluctuations can also cause neurological symptoms such as migraines, numbness, and tingling sensations. In addition, gestational diabetes, which can develop during the second trimester, has been associated with an increased risk of neurological disorders such as AD and other dementias later in life (Table 1).

During the third trimester, hormone levels reach their peak, and the body prepares for childbirth. The hormone levels remain high throughout this period, with the highest levels of estrogen being produced by the placenta. Estrogen plays a vital role in the development of the fetus and prepares the body for childbirth by softening the cervix and relaxing the pelvic muscles. At this stage, oxytocin, and prolactin, which are responsible for the development of the mother's breast, lactation and uterine contractions during childbirth, also promote bonding and social behavior, which can have a positive effect on the CNS. However, high levels of estrogen and progesterone can also cause neurological symptoms such as migraines, depression, and anx-

Table 1. Beyond Morning Sickness: Hormones and Neurological Symptoms in Pregnancy.

Pregnancy periods	Hormones levels	Function	Neurological symptoms	Non-neurological symptoms	References
First Trimester	Progesterone++	Prepares the mother's uterus lining for the egg to implant by thickening and nourishing the endometrium. It also acts as a muscle relaxant, preventing the mother's uterus from contracting until the onset of labor.	Mood swings, (e.g., Anger, sadness, happiness, and anxiety).	Morning sickness (e.g., feeling of nausea and vomiting, breast tenderness, and frequent urination), constipation, and classic irritability during the pre-menstrual period.	[88,145, 146]
	Estrogen++	Promotes an increase in blood flow to the uterus. This increased blood flow is important for nourishing the developing baby and maintaining the endometrial lining, which is vital for the baby's growth and development. This increased blood flow also helps to support the placenta, which is responsible for exchanging nutrients and waste products between the mother and the fetus.	Headaches, dizziness, and nausea.	Swelling of the mucous membranes in the nasal passage, leading to a stuffy nose, experience achy and tender breasts, feeling of the urgent and frequent need to urinate.	[147–150]
	Human chorionic gonadotropin++	Placenta formation and the maintenance of early pregnancy.	An exquisitely refined olfactory capacity, capable of detecting the subtlest of scents with remarkable acuity and precision, transcends the normative boundaries of the average human sense of smell.	Morning sickness.	[151–153]
	Thyroid hormones++	Regulating the cellular metabolism in the maternal body, ensuring the proper uptake and utilization of nutrients required for the healthy growth and development of the fetus, supporting the baby's neurodevelopment and bone development, contributing to the formation of the fetal brain and skeletal system.	Anxiety, nervousness, abnormal brain growth, sensitivity to cold or heat, and difficulty concentrating or remembering.	Fatigue and weakness, weight gain or loss, difficulty sleeping, changes in appetite or digestion, dry skin or hair, muscle weakness or cramps, and menstrual irregularities.	[154–157]
Second Trimester	Progesterone+++	Maintains pregnancy and prevents preterm birth.	Migraines, numbness, and tingling sensations.	Melasma, linea nigra, nipples darkening, pronounced moles and freckles, rapid hair growth.	[158–162]
Second Trimester	Estrogen+++	Promotes the growth and development of the fetal brain	Headaches, dizziness, and nausea	-	
	Relaxin+++	Helps to loosen the ligaments and joints in the pelvis to prepare for childbirth.	Indirectly affect the nervous system by causing changes in posture and gait due to the increased flexibility and mobility of the joints.	Back pain, sprains or strains, swelling in the joints, increased risk of varicose veins, and increased susceptibility to falls.	[163–165]

Table 1. Continued.

Pregnancy periods	Hormones levels	Function	Neurological symptoms	Non-neurological symptoms	References
	Cortisol+++	Helps to regulate fetal development, including the growth of the lungs, liver, and other organs, helps the mother cope with stressors during pregnancy, regulates glucose metabolism, which is especially important during pregnancy when the body's demand for glucose increases, and suppresses immune function, which helps prevent the mother's body from rejecting the fetus as a foreign object.	Anxiety and depression.	Fatigue, increased appetite and weight gain, stretch marks, high blood pressure, gestational diabetes, and redness in the face and cheeks.	[166–171]
	Human placental lactogen+++	Supporting fetal growth, regulating glucose metabolism, stimulating breast development, promoting protein synthesis, and reducing maternal insulin sensitivity.	Memory defects.	Increased thirst and hunger, frequent urination, fatigue, obesity, and gestational diabetes.	[172–175]
Third Trimester	Progesterone++++ Estrogen++++	Maintaining the uterine lining, suppressing contractions, promoting lung development, preparing the breasts for lactation, and supporting the mother's immune system during pregnancy, which is important for protecting both the mother and the fetus from infections.	Migraines, depression, anxiety, stroke.	Swelling around ankles and feet, acid reflux, heartburn.	[158–162]
	Estrogen++++	Maintaining cervical mucus, stimulating uterine growth, preparing for labor, and supporting fetal development.	-	Fatigue, heartburn, Braxton Hicks contractions, increased vaginal discharge, swelling in the legs, feet, and hands, breast changes such as increased size, tenderness, and the appearance of colostrum.	
	Relaxin+++	Soften and relax the cervix in preparation for labor and delivery, helps to relax the ligaments in the pelvis, allowing it to expand during childbirth, facilitate the delivery of the baby by increasing the flexibility of the pelvic bones and allowing the baby's head to pass through the birth canal more easily, and stimulate contractions of the uterus during labor, helping to push the baby out.	Social behavior defect.	Cause the joints in the body to become more flexible, which can lead to pain and instability, back pain, increases vaginal discharge, heartburn and acid reflux, and swelling in the feet, ankles, and hands.	[163–165]
	Prolactin+++	Stimulates the growth and development of the mammary glands in preparation for breastfeeding, production of breast milk, support the immune system of both the mother and the developing fetus during pregnancy, cause a calming effect on the mother, promoting relaxation and bonding with the developing baby, stimulate contractions and promote the delivery of the baby.	Changes in mood, behavior, and higher processes such as cognition.	Breast enlargement, tenderness, and sensitivity, darkening of the skin around the nipples, areolas, and vulva.	[148,174, 176–179]

Table 1. Continued.

Pregnancy periods	Hormones levels	Function	Neurological symptoms	Non-neurological symptoms	References
	Oxytocin+++	Inducing and regulating labor contractions during childbirth, promote the formation of a strong emotional bond between mother and baby, stimulates the release of breast milk from the mammary glands, and helps to facilitate breastfeeding after delivery.	Postpartum depression.	Braxton Hicks contractions, nesting, feelings of love and attachment to the developing baby.	[180–183]
Postpartum	Estrogen+, Progesterone+, Relaxin+, Human cho-rionic gonad-otropin+, human placental lactogen+	Help manage pain.	-	Sleep deprivation, hypertension.	[166,184–189]
	Prolactin+++	Stimulates the release of milk from the milk ducts. Breastfeeding, mood regulation, act as a natural form of contraception, as high levels of prolactin can suppress ovulation and delay the return of menstruation after childbirth.	-	-	
	Cortisol+++	Involved in the body's response to stress.	Development of postpartum depression and anxiety.	Disruptions in sleep pattern.	
	Epinephrine and norepinephrine+++	Cause the heart rate to increase and blood pressure to rise, which can help to prepare the mother's body for the physical demands of childbirth, promote feelings of alertness and energy, help the mother to cope with the physical and emotional stress of labor and delivery, and cause delayed breastfeeding.	-	-	
	Beta-endorphins +++	Helping to relieve the pain and discomfort associated with childbirth and the postpartum recovery period, helping to reduce feelings of anxiety and depression, promoting the initiation and maintenance of breastfeeding after delivery, promoting bonding between the mother and the newborn, as well as enhancing feelings of love and attachment.	-	-	
	Oxytocin+++	Continues to play a role in postpartum recovery, helping the uterus to contract and return to its pre-pregnancy size	Postpartum depression.	-	

iety. In addition, preeclampsia (which, as we mentioned earlier in the related section, is a condition that develops in the third trimester), has been associated with an increased risk of neurological disorders including but not limited to cerebrovascular diseases and epilepsy.

After childbirth, estrogen, progesterone, and relaxin levels drop rapidly, and the beta-endorphins, epinephrine, norepinephrine, prolactin, cortisol, and oxytocin levels increase. Such a drop in the levels of indicated hormones can cause a range of neurological symptoms such as mood swings, depression, and anxiety, which are collectively known as postpartum depression (Table 1).

Animal models, such as rats, mice, and sheep, have been used to investigate the effects of hormonal changes on brain plasticity during pregnancy and postpartum. The results of these studies suggest that these hormones can significantly modulate the process of neuroplasticity, including adult neurogenesis, in many brain regions, such as the hypothalamus and hippocampal formation [20,190]. It is important to note that these changes in brain plasticity during pregnancy and postpartum are not solely limited to animal models. Studies in humans have also demonstrated significant structural and functional changes in the brain during this time. For example, there is evidence of increased gray matter volume in regions associated with social cognition, such as the amygdala, insula, and prefrontal cortex, during pregnancy and postpartum [191–193].

Furthermore, there has been a growing interest in recent years in understanding the potential relationship between pregnancy hormones and the risk of developing AD and related dementias [194,195]. Estrogen has been shown to play an important role in brain health [196], and some studies have suggested that it may help protect against dementia [197]. However, a study has also found that women who had given birth to five or more children were twice as likely to develop AD and other dementia compared to women who had only given birth to one or two children [18]. It is therefore suggested that the hormonal changes associated with pregnancy, as well as the stresses of raising multiple children, may contribute to the increased risk of developing dementia.

Studies have also found that women who had experienced preeclampsia during pregnancy had a significantly increased risk of developing dementia later in life [92,198]. Studies have found that the risk of stroke is higher in the postpartum period compared to the non-pregnant state. This increased risk is thought to be due to changes in blood clotting and blood pressure during pregnancy, which can increase the likelihood of stroke [199].

Similarly, a study has also linked pregnancy to an increased risk of PD [200,201]. Dopamine is a neurotransmitter that is involved in movement, and changes in its levels due to the loss of dopaminergic neurons can lead to the development of PD [202–205]. These findings suggest that pregnancy-induced biological changes may cause the loss of dopaminergic neurons and the resulting deficiency of dopamine that leads to the development of PD. However, to make it more complicated, the occurrence of PD during pregnancy is very rare, and PD is more prevalent in males than females.

Epilepsy is another neurological disorder that has been linked to pregnancy. Women with epilepsy are at increased risk of seizures during pregnancy, particularly in the first trimester [15]. Menstrual disorders, polycystic ovaries, and infertility have been described among women with epilepsy [206–208]. These findings suggest that hormonal changes during pregnancy may affect brain functions and cause the development of epilepsy.

MS is a chronic neurological disorder that affects the CNS. While pregnancy is not thought to cause MS, studies have shown that women with MS may experience fewer symptoms during pregnancy [209]. However, the postpartum period can be a particularly challenging time for women with MS [11,12]. These studies suggest that the hormonal changes that occur after childbirth can trigger a relapse of symptoms.

Pregnancy has also been linked to an increased risk of suicide. This is thought to be due to the changes in hormone levels that occur during pregnancy and in the postpartum period, which can lead to mood changes and depression [13, 14].

Throughout pregnancy, Mϕs and dendritic cells (DCs) populations undergo longitudinal changes in phenotype and function. MOs play a critical role in the initiation and regulation of immune responses, while Mϕs are involved in tissue repair and maintenance of immune tolerance. The immune clock of pregnancy orchestrates dynamic waves of carefully orchestrated changes that involve the development of MLR-Bf, APCA, AITA, NK cells, Treg, and massive production of pregnancy-specific glycoproteins (PSGs) such as PSG1, PSG6, PSG6N, and PSG11 and their link to massive production of anti-inflammatory and regulatory cytokines, such as interleukin 4 (IL4), IL6, TGFβ1 and the reduction in generation of pro-inflammatory cytokines and autoantibodies, i.e., anti-phospholipid antibody (APLA), anti-nuclear antibody (ANA), anti-cardiolipin antibody (ACLA), and anti-prothrombin antibody (APTA) as summarized in Table 2 (Ref. [85,131–134,210–293]).

However, inflammatory immune responses triggered by certain microorganisms (e.g., human immunodeficiency virus, Zika virus, severe acute respiratory syndrome coronavirus-2, Listeria monocytogenes, malaria, bacterial vaginosis, chlamydia, mycoplasma, and intestinal helminths) and antibodies to specific antigens, (e.g., APTA, ANA, and ACLA) can lead to the dysregulation of immune cells (e.g., Mϕs, NK cells, effector T cells, Treg, iNKT cells, ILCs, and B cell subsets), and reduced production of protective antibodies (e.g., MLR-Bf, APCA, AITA) and certain cytokines (e.g., IL4, IL6, inter-

Table 2. Innate and Adaptive Immune Responses Support a Healthy Pregnancy.

Immune players	Status	References
MOs	(++)	[213,214]
Mϕs	(++)	[215–219]
DCs	(+)	[215,220]
NK cells	(+++)	[213,217,221–223]
CD3$^+$ CD8$^+$ T cells	(-)	[213,224–227]
Treg (CD4+ CD25+, CD8+ CD25+, CD56+)	(+++)	[213,224,228–236]
ILCs (CD15- CD14- CD3- CD19- CD56- CD11b- CD127+ cells) and their subsets (ILC1, T-bet+ ILCs; ILC2, GATA3+ ILCs; and ILC3, RORγt+ ILCs)	(-)	[213,237]
B and B1B cells	(-)	[212,213]
PSGs	(+++)	[213,238–242]
IFN γ	(-)	[224,243–245]
TNFα	(-)	[224,243,244]
IL1β	(-)	[245,246]
IL2	(-)	[243,246]
IL3	(-)	[245,247]
IL4	(+++)	[224,243,246,248]
IL5	(++)	[243,245,249]
IL6	(+++)	[243–245]
IL8	(-)(++)	[213,246]
IL9	(+)	[245,250]
IL10	(+/-)	[211,224,243–245]
IL12 p40	(+)	[211,213,251]
IL12p70	(-)	[213,224,246,252,253]
IL17	(++)	[85,210,246,254–258]
IL18	(+/-)	[211,246,259]
TGFβ1	(+++)	[244,245,260–263]
C1q	(+)	[264–270]
C1-INH	(-)	[264]
C3	(+)	[264,271–275]
C3a	(+)	[264,274,276]
C3d	(+)	[267,268,270,275]
C4	(++)	[266,267,277]
C4a	(+++)	[213,276,278]
C4d	(+)	[213,264,274]
C4BP	(+)	[268,270]
C5a	(+)	[213,264,276,278]
C6	(+)	[267,279]
C7	(+)	[279]
C8	(+)	[279]
C9	(+)	[213,264,267,268,270,274,275]
sC5b9	(+)	[264,274,280]
Factor H	(+)	[213,264,268,270,274]
APLA	(-)	[224,281–283]
ANA	(-)	[284,285]
ACLA	(-)	[281,286]
APTA	(-)	[287,288]
MLR-Bf	(+++)	[133,134,289,290]
APCA	(+++)	[290–293]
AITA	(+++)	[131,132,291]

MOs, monocytes; Mϕs, macrophages; DCs, dendritic cells; NK, natural killer; Treg, T regulatory cells; ILCs, innate lymphoid cells; PSGs, pregnancy-specific glycoprotein; IFNγ, interferon gamma; TNFα, tumor necrosis factor alpha; IL, interleukin; TGFβ1, transforming growth factor beta1; C, complement; APLA, anti-phospholipid antibody; ANA, anti-nuclear antibody; ACLA, anti-cardiolipin antibody; APTA, anti-prothrombin antibody; MLR-Bf, mixed lymphocyte reaction blocking factor; APCA, anti-paternal cytotoxic antibody; AITA, anti-idiotypic antibody. +++, higher levels; ++, medium levels; +, lower levels; -, absent.

leukin 10 (IL10), and TGFβ1). This dysregulation creates an environment that favors the excessive generation of pro-inflammatory cytokines such as interferon-gamma (IFNγ), IL1β, tumor necrosis factor-alpha (TNFα), IL6, interleukin 17 (IL17), and complement proteins which lead to adverse pregnancy outcomes, including recurrent spontaneous abortion, preterm birth, and pre-eclampsia [210–212,294–309].

The excessive production of such pro-inflammatory cytokines (e.g., IFNγ, IL1β, TNFα, IL6, IL17) can activate endothelial cells and induce the expression of adhesion molecules, such as intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1). These adhesion molecules promote the adhesion and transmigration of immune cells, including Mϕs and T cells, across the blood-brain barrier (BBB). Once inside the brain, these immune cells release additional pro-inflammatory cytokines and reactive oxygen species, leading to BBB disruption, neuroinflammation, and the development of neurodegenerative diseases [310–329].

Complement proteins, particularly complement component 3 (C3) and complement component 5 (C5) can also contribute to BBB damage. Activation of the complement system generates anaphylatoxins, such as C3a and C5a, which can increase vascular permeability and promote the recruitment of immune cells to the site of inflammation. Additionally, the membrane attack complex (MAC), formed by complement proteins, can directly lyse endothelial cells, leading to BBB disruption [318,320,330–335].

The findings of this study suggest that damage to the BBB and the persistent neuroinflammation caused by the excessive production of pro-inflammatory cytokines and complement proteins can contribute to the development of various neurological diseases during pregnancy and in the postpartum period.

Conclusions

The dysregulated hormonal and immune response triggered by certain infections and autoimmune conditions during pregnancy can contribute to the development of neuroinflammation, increasing the risk of CNS diseases. However, the exact mechanisms by which the abnormal hormonal and immune response triggers BBB damage are poorly defined and require further investigation.

Current research findings indicate that hormonal and physiological changes in pregnancy or early-stage pregnancy failure can lead to the excessive production of pro-inflammatory cytokines, such as IFNγ, TNFα, IL1α, IL1β, IL6, and IL17, as well as autoantibodies and complement proteins. These inflammatory mediators may contribute to BBB damage, cellular death, and the development of various CNS diseases.

Ongoing research aims to uncover the interplay between hormones, immunological factors, and physiological processes that are critical for the development of CNS diseases during pregnancy. However, despite these efforts, many questions remain unanswered, including the specific roles of hormonal defects and innate and adaptive immune responses in disease progression. It is important to recognize that while studies suggest a link between pregnancy and CNS diseases, the evidence is not yet conclusive. Other factors, such as genetics, lifestyle, and environmental influences, may also contribute to the development of CNS diseases.

It is crucial to understand that the findings regarding the relationship between pregnancy and CNS diseases are still emerging, and further research is necessary to fully comprehend the potential links between them. In the meantime, individuals can take steps to maintain overall brain health during pregnancy. This includes engaging in regular physical activity, consuming a healthy and balanced diet, getting sufficient sleep, and participating in activities that challenge the brain, such as reading, puzzles, and social interactions. For those concerned about the potential effects of pregnancy on their risk of developing CNS diseases, it is advisable to seek personalized advice and support from a medical professional.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

LM played a crucial role in conceiving the study, demonstrating their insightful approach to the research question at hand. LM actively participated in the writing process, including the meticulous preparation, collection, and extensive assessment of the original literature, which shaped the structure and content of the paper, enabling the effective communication of the research findings. AFM and VST prepared the Tables. AMS performed writing, analysis, and interpretation of published data as well as undertook the task of conducting a critical review of the entire document, detailed scrutinizing its content and structure. AMS's valuable insights and contributions helped refine the manuscript, ensuring its clarity and coherence. MKP played a pivotal role in the inception and execution of the study, displaying a thoughtful approach throughout the entire process. His involvement encompassed various crucial aspects, including the conceptualization of the study, the preparation, collection, and comprehensive evaluation of the original literature, as well as the design of tables to enhance data presentation. Furthermore, MKP actively engaged in the writing and rebuttal process, diligently addressing the reviewer's comments and suggestions. In the final stages of the project, MKP assumed the responsibility of completing the editing process, meticulously refining the manuscript, and ensuring its adherence to high standards of academic writing and finalization of the manuscript. All authors contributed to editorial changes in the manuscript, read and approved the final manuscript, participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Manoj Kumar Pandey is serving as one of the Editorial Board Members of this journal. We declare that Manoj Kumar Pandey had no involvement in the peer review of this article and has no access to information regarding its peer review.

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